

DETAILED ACTION

Status of Claims

Claim 1 has been amended. Claims 46-49 are newly added. Claims 1-30 and 35-49 are pending, of which claims 16, 17, 25, 26, 35-40, 43 and 44 are withdrawn from consideration at this time as being drawn to a non-elected invention. Claims 1-15, 18-24, 27-30, 41, 42 and 45-49 are readable upon the elected invention and are examined herein on the merits for patentability.

Response to Arguments

Applicant's arguments have been fully considered but are moot in view of the new ground(s) of rejection, made in view of newly discovered references and necessitated by claim amendment.

Claim Objections

Claim 49 is objected to because of the following informalities: the claim appears to contain a typographical error wherein the targeting ligand *id* covalently bound to the amphiphilic material. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148

USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 46-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 2000143550 in view of WO 03/05029.

JP 2000143550 teaches magnetic substance particles (preferably Fe_2O_3 , Fe_3O_4 , etc.) are adsorbed onto the surfaces of microbubbles coated with a carboxylic acid salt (preferably sodium laurate, etc.). The contrast medium is preferably used by coating the magnetic substance particles with a cationic surfactant. The movement of the contrast medium can be controlled by external magnetic field. Thereby, the microbubbles can timely be introduced into sites causing problems in the human body, e.g. specific regions such as tumors in various kinds of internal organs or early cancers and diseases can accurately be observed and diagnosed by ultrasonic waves (abstract). See also paragraphs 0014-0028 for working examples, association between including magnetite particles with cationic surfactant (e.g. DCPL) coating and sodium stearate microbubbles in aqueous solution.

The magnetic particles electrostatically associated with the microbubbles in the example of JP 2000143550 are 300 nm, rather than 100 nm or less, as claimed.

WO 03/05029 teaches superparamagnetic nanoparticles of magnetite. Particles are highly crystalline in the 10-250, preferably 50 to 150 nm diameter range, exhibiting superparamagnetic characteristics with a saturation magnetization of 62 emu/g. The particles are stabilized with a coating such as dextran. These particles have potential applications in biological cell separations, drug delivery, and nondestructive clinical diagnosis (abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify particle size of the magnetic particles taught by JP 2000143550 which are used for magnetically guiding microbubbles, to employ a particle size such as 50 nm. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because WO 03/05029 shows that particles in the range of 50-150 nm are preferable for use in magnetic drug delivery or biological cell separation.

Regarding the claim limitations wherein the component associated with the microvesicle is a supermolecular structure formed by association of a plurality of molecules, which bears a second overall net charge opposite in sign to said first net charge, consists essentially of molecules of a biocompatible surface active agent, optionally comprises a targeting ligand and/or a bioactive agent and has a diameter of 100 nm or lower, it is noted that the instant specification does not exclude magnetic particles from what materially affects the basic and novel characteristics of the second

component. For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" has been construed as equivalent to "comprising," see MPEP 211.03.

The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976) (emphasis in original) (Prior art hydraulic fluid required a dispersant which appellants argued was excluded from claims limited to a functional fluid "consisting essentially of" certain components. In finding the claims did not exclude the prior art dispersant, the court noted that appellants' specification indicated the claimed composition can contain any well-known additive such as a dispersant, and there was no evidence that the presence of a dispersant would materially affect the basic and novel characteristic of the claimed invention. The prior art composition had the same basic and novel characteristic (increased oxidation resistance) as well as additional enhanced detergent and dispersant characteristics.). "A 'consisting essentially of' claim occupies a middle ground between closed claims that are written in a 'consisting of' format and fully open claims that are drafted in a 'comprising' format." *PPG Industries v. Guardian Industries*, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998). See also *Atlas Powder v. E.I. duPont de Nemours & Co.*, 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984); *In re Janakirama-Rao*, 317 F.2d 951, 137 USPQ 893 (CCPA 1963); *Water Technologies Corp. vs. Calco, Ltd.*, 850 F.2d 660, 7 USPQ2d 1097 (Fed. Cir. 1988). For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." See, e.g., *PPG*, 156 F.3d at 1355, 48 USPQ2d at 1355 ("PPG could have defined the scope of the phrase 'consisting essentially of' for purposes of its patent by making clear in its specification what it regarded as constituting a material change in the basic and novel characteristics of the invention.").

Futhermore, the claim recites that the second component may optionally comprise a targeting ligand and/or a bioactive agent. A magnetic particle can be interpreted to meet either of those limitations. For example, a magnetic particle can be interpreted as a targeting ligand because it can be controlled by external magnetic field to a specific target site. A magnetic particle can be interpreted as a bioactive agent, for

example it could have therapeutic use as in magnetic hyperthermia. Regarding claims 48 and 49, targeting ligand is recited as optional.

Claims 1, 4-15, 18, 19, 27-30, 42 and 46-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eriksen *et al.* (US 2004/0146462), as evidenced by The Free Dictionary, "microemulsion," <http://encyclopedia2.thefreedictionary.com/Microemulsion>.

Eriksen teaches a combined preparation for simultaneous, separate or sequential use as a contrast agent in ultrasound imaging, said preparation comprising: i) a first composition which is an injectable aqueous medium comprising dispersed gas and material serving to stabilise said gas; and ii) a second composition which is an injectable oil-in-water emulsion wherein the oil phase comprises a diffusible component capable of diffusion in vivo into said dispersed gas so as at least transiently to increase the size thereof, said composition further comprising material serving to stabilise said emulsion, characterised in that material present at the surfaces of the dispersed gas phase and material present at the surfaces of the dispersed oil phase have opposite charges and thereby have affinity for each other (claim 1). See also paragraphs 20-47. The first composition includes gas microbubbles (paragraphs 0030-0033). The dispersed oil phase in the second composition may comprise any appropriate diffusible component which is at least partially insoluble in and immiscible with water. The diffusible component in such emulsions is advantageously a liquid at processing and storage temperature, while being a gas or exhibiting a substantial vapour pressure at

body temperature. Specific examples of emulsifiable diffusible components are preferably perfluorocarbons (paragraph 0038). The emulsion-stabilising material may typically comprise one or more surfactants (paragraph 0041). The diffusible component may be a microemulsion (paragraph 0047). The emulsion component is considered to be within the scope of the instantly claimed "supermolecular structure formed by the association of a plurality of molecules." Peptide containing emulsions including surfactants are disclosed in the examples (Table 1, e.g. preparation 24). See also Examples 10-27 including negatively charged perfluorobutane gas microbubbles (stabilized by hydrogenated phosphatidylserine) and positively charged emulsions; especially Ex. No 15. Therapeutic agents are disclosed as part of the preparation (claim 20). Targeting vectors are taught in paragraph 0085. Representative drugs include DNA, etc. (i.e. charged) (paragraph 0086). The contrast agents may serve as vehicles for other contrast-enhancing moieties (x-ray magnetic resonance, scintigraphic) (paragraph 0087-0088). If desired, the diffusible component may also be formulated as a microemulsion. Such systems are advantageous by virtue of their thermodynamic stability and the fact that the diffusible component is in practice uniformly distributed throughout the aqueous phase; microemulsions therefore have the appearance of solutions but may exhibit the properties of emulsions as regards the partial pressure of the dispersed phase (paragraph 0047).

With regard to claim 5, distearoylphosphatidylcholine is also included emulsions comprising positively charged surface material and are considered to be "bioactive" in that the component functions as a surfactant in a biological system (paragraph 0154).

With regard to claim 6, preparation 2 is disclosed, including microbubbles comprising 1,2-distearoyl-3-trimethyl-ammoniumpropane and distearoylphosphatidylcholine, which are considered to be "bioactive" in that the component functions as a surfactant in a biological system.

With regard to claims 9-11, 0.2 μl gas/kg body weight negatively charged perfluorobutane gas dispersion was combined with 0.1 μl gas/kg body weight positively charged perfluorodimethylcyclobutane emulsion.

Eriksen does not specifically exemplify a supermolecular structure having a particle size of 100 nm as the diffusible component. However, Eriksen teaches that if desired, the diffusible component may also be formulated as a microemulsion. Such systems are advantageous by virtue of their thermodynamic stability and the fact that the diffusible component is in practice uniformly distributed throughout the aqueous phase (paragraph 0047).

The Free Dictionary recites that microemulsion is defined as:
microemulsion: a thermodynamically stable dispersion of two immiscible liquids, stabilized by surfactants; it is typically clear because the dispersed droplets are less than 100 nanometers in diameter. McGraw-Hill Dictionary of Scientific & Technical Terms, 6E, Copyright © 2003 by The McGraw-Hill Companies, Inc.

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide preparations as disclosed by Eriksen comprising negatively charged gas microbubbles and positively charged emulsions in which the emulsion component has a particle size of 100 nm or less. One would have been motivated to do

so, and would have had a reasonable expectation of success in doing so because Eriksen teaches that if desired, the diffusible component may be formulated as a microemulsion. Such systems are advantageous by virtue of their thermodynamic stability and the fact that the diffusible component is in practice uniformly distributed throughout the aqueous phase; microemulsions therefore have the appearance of solutions but may exhibit the properties of emulsions as regards the partial pressure of the dispersed phase (paragraph 0047). The Free Dictionary reference is included to show that microemulsion inherently has particle size less than 100 nm. With regard to claims 28-30, the Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same functional characteristics of the claimed product. The claims are descriptive of the zeta potential of the assembly, and thus would be an inherent property of the claimed composition. In the absence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 U.S.P.Q.2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), *Ex parte Gray*, 10 USPQ2d 1922, 1923 (PTO Bd. Pat. App. & Int.) and *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). Since Eriksen teaches compositions meeting the structural requirements of the instant claims, it is interpreted absent evidence to the contrary that such formulations would be capable of achieving claimed functional property (zeta potential). Regarding claims 48 and 49, targeting ligand is recited as optional.

Claims 1-15, 18, 19, 27-30, 42 and 46-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eriksen *et al.* (US 2004/0146462) in view of Kunz *et al.* (US 2002/0169138).

Eriksen teaches a combined preparation for simultaneous, separate or sequential use as a contrast agent in ultrasound imaging, said preparation comprising: i) a first composition which is an injectable aqueous medium comprising dispersed gas and material serving to stabilise said gas; and ii) a second composition which is an injectable oil-in-water emulsion wherein the oil phase comprises a diffusible component capable of diffusion in vivo into said dispersed gas so as at least transiently to increase the size thereof, said composition further comprising material serving to stabilise said emulsion, characterised in that material present at the surfaces of the dispersed gas phase and material present at the surfaces of the dispersed oil phase have opposite charges and thereby have affinity for each other (claim 1). See also paragraphs 20-47. The first composition includes gas microbubbles (paragraphs 0030-0033). The dispersed oil phase in the second composition may comprise any appropriate diffusible component which is at least partially insoluble in and immiscible with water. The diffusible component in such emulsions is advantageously a liquid at processing and storage temperature, while being a gas or exhibiting a substantial vapour pressure at body temperature. Specific examples of emulsifiable diffusible components are preferably perfluorocarbons (paragraph 0038). The emulsion-stabilising material may typically comprise one or more surfactants (paragraph 0041). The diffusible component

may be a microemulsion (paragraph 0047). The emulsion component is considered to be within the scope of the instantly claimed "supermolecular structure formed by the association of a plurality of molecules." Peptide containing emulsions including surfactants are disclosed in the examples (Table 1, e.g. preparation 24). See also Examples 10-27 including negatively charged perfluorobutane gas microbubbles (stabilized by hydrogenated phosphatidylserine) and positively charged emulsions; especially Ex. No 15. Therapeutic agents are disclosed as part of the preparation (claim 20). Targeting vectors are taught in paragraph 0085. Representative drugs include DNA, etc. (i.e. charged) (paragraph 0086). The contrast agents may serve as vehicles for other contrast-enhancing moieties (x-ray magnetic resonance, scintigraphic) (paragraph 0087-0088). If desired, the diffusible component may also be formulated as a microemulsion. Such systems are advantageous by virtue of their thermodynamic stability and the fact that the diffusible component is in practice uniformly distributed throughout the aqueous phase; microemulsions therefore have the appearance of solutions but may exhibit the properties of emulsions as regards the partial pressure of the dispersed phase (paragraph 0047).

With regard to claim 5, distearoylphosphatidylcholine is also included emulsions comprising positively charged surface material and are considered to be "bioactive" in that the component functions as a surfactant in a biological system (paragraph 0154).

With regard to claim 6, preparation 2 is disclosed, including microbubbles comprising 1,2-distearoyl-3-trimethyl-ammoniumpropane and

distearoylphosphatidylcholine, which are considered to be "bioactive" in that the component functions as a surfactant in a biological system.

With regard to claims 9-11, 0.2 μl gas/kg body weight negatively charged perfluorobutane gas dispersion was combined with 0.1 μl gas/kg body weight positively charged perfluorodimethylcyclobutane emulsion.

Eriksen does not specifically exemplify a supermolecular structure having a particle size of 100 nm as the diffusible component. However, Eriksen teaches that if desired, the diffusible component may also be formulated as a microemulsion. Such systems are advantageous by virtue of their thermodynamic stability and the fact that the diffusible component is in practice uniformly distributed throughout the aqueous phase (paragraph 0047).

Kunz teaches that microemulsion delivery vehicles can be o/w, w/o or bicontinuous and are characterized as being self-emulsifying, dispersions of oil and an oil-immiscible material stabilized by interfacial films of surface-active agents. That is, the microemulsions form spontaneously without the need for energy input. The microemulsions are further generally characterized by small average droplet sizes, from about 0.1 nm to about 200 nm, and in one embodiment have a diameter of less than about 100 nm. They are further characterized by their wide range of temperature stability, typically from about 5 C to about 100 C, and they appear to be thermodynamically stable. Microemulsions are also relatively insensitive to pH or ionic strength of an aqueous phase when nonionic surfactants are used. Furthermore, the microemulsions are usually transparent or opalescent when viewed by both

macroscopic and microscopic means. Undisturbed, they are optically isotropic when examined under polarized light (paragraph 0110).

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide preparations as disclosed by Eriksen comprising negatively charged gas microbubbles and positively charged emulsions in which the emulsion component has a particle size of 100 nm or less. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because Eriksen teaches that if desired, the diffusible component may be formulated as a microemulsion. Such systems are advantageous by virtue of their thermodynamic stability and the fact that the diffusible component is in practice uniformly distributed throughout the aqueous phase; microemulsions therefore have the appearance of solutions but may exhibit the properties of emulsions as regards the partial pressure of the dispersed phase (paragraph 0047). One of ordinary skill would have had a reasonable expectation of success that the microemulsion would have a size less than 100 nm because Kunz teaches that microemulsions are further generally characterized by small average droplet sizes, from about 0.1 nm to about 200 nm, and in one embodiment have a diameter of less than about 100 nm. With regard to claims 28-30, the Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same functional characteristics of the claimed product. The claims are descriptive of the zeta potential of the assembly, and thus would be an inherent property of the claimed composition. In the absence to the contrary, the burden is upon the

applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 U.S.P.Q.2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), *Ex parte Gray*, 10 USPQ2d 1922, 1923 (PTO Bd. Pat. App. & Int.) and *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). Since Eriksen teaches compositions meeting the structural requirements of the instant claims, it is interpreted absent evidence to the contrary that such formulations would be capable of achieving claimed functional property (zeta potential). Regarding claims 48 and 49, targeting ligand is recited as optional.

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Eriksen teaches a combined preparation for simultaneous, separate or sequential use as a contrast agent in ultrasound imaging, said preparation comprising: i) a first composition which is an injectable aqueous medium comprising dispersed gas and material serving to stabilise said gas; and ii) a second composition which is an injectable oil-in-water emulsion wherein the oil phase comprises a diffusible component capable of diffusion in vivo into said dispersed gas so as at least transiently to increase the size thereof, said composition further comprising material serving to stabilise said emulsion, characterised in that material present at the surfaces of the dispersed gas

phase and material present at the surfaces of the dispersed oil phase have opposite charges and thereby have affinity for each other (claim 1). See also paragraphs 20-47. The first composition includes gas microbubbles (paragraphs 0030-0033). The dispersed oil phase in the second composition may comprise any appropriate diffusible component which is at least partially insoluble in and immiscible with water. The diffusible component in such emulsions is advantageously a liquid at processing and storage temperature, while being a gas or exhibiting a substantial vapour pressure at body temperature. Specific examples of emulsifiable diffusible components are preferably perfluorocarbons (paragraph 0038). The emulsion-stabilising material may typically comprise one or more surfactants (paragraph 0041). The diffusible component may be a microemulsion (paragraph 0047). The emulsion component is considered to be within the scope of the instantly claimed "supermolecular structure formed by the association of a plurality of molecules." Peptide containing emulsions including surfactants are disclosed in the examples (Table 1, e.g. preparation 24). See also Examples 10-27 including negatively charged perfluorobutane gas microbubbles (stabilized by hydrogenated phosphatidylserine) and positively charged emulsions; especially Ex. No 15. Therapeutic agents are disclosed as part of the preparation (claim 20). Targeting vectors are taught in paragraph 0085. Representative drugs include DNA, etc. (i.e. charged) (paragraph 0086). The contrast agents may serve as vehicles for other contrast-enhancing moieties (x-ray magnetic resonance, scintigraphic) (paragraph 0087-0088). If desired, the diffusible component may also be formulated as a microemulsion. Such systems are advantageous by virtue of their thermodynamic

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Ostensen teaches that diffusible components for administration orally or by injection may, for example, be formulated as solutions in or mixtures with water and/or one or more water-miscible and physiologically acceptable organic solvents, such as ethanol, glycerol or polyethylene glycol; dispersions in an aqueous medium, for example as the oil phase or a constituent of the oil phase of an oil-in-water emulsion; *microemulsions*, i.e. systems in which the substance is effectively dissolved in the hydrophobic interiors of *surfactant micelles* present in an aqueous medium (column 7, line 40).

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide preparations as disclosed by Eriksen comprising negatively charged gas microbubbles and positively charged emulsions in which the emulsion component has a particle size of 100 nm or less. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because Eriksen teaches that if desired, the diffusible component may be formulated as a microemulsion. Such systems are advantageous by virtue of their thermodynamic stability and the fact that the diffusible component is in practice uniformly distributed throughout the aqueous phase; microemulsions therefore have the appearance of solutions but may exhibit the properties of emulsions as regards the partial pressure of

the dispersed phase (paragraph 0047). The Free Dictionary reference is included to show that microemulsion inherently has particle size less than 100 nm. The Ostensen reference is included to show that microemulsion inherently includes micelle. With regard to claims 28-30, the Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same functional characteristics of the claimed product. The claims are descriptive of the zeta potential of the assembly, and thus would be an inherent property of the claimed composition. In the absence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 U.S.P.Q.2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), *Ex parte Gray*, 10 USPQ2d 1922, 1923 (PTO Bd. Pat. App. & Int.) and *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). Since Eriksen teaches compositions meeting the structural requirements of the instant claims, it is interpreted absent evidence to the contrary that such formulations would be capable of achieving claimed functional property (zeta potential). Regarding claims 48 and 49, targeting ligand is recited as optional.

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ethanol, glycerol or polyethylene glycol; dispersions in an aqueous medium, for example as the oil phase or a constituent of the oil phase of an oil-in-water emulsion; *microemulsions*, i.e. systems in which the substance is effectively dissolved in the hydrophobic interiors of *surfactant micelles* present in an aqueous medium (column 7, line 40).

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide preparations as disclosed by Eriksen comprising negatively charged gas microbubbles and positively charged emulsions in which the emulsion component has a particle size of 100 nm or less. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because Eriksen teaches that if desired, the diffusible component may be formulated as a microemulsion. Such systems are advantageous by virtue of their thermodynamic stability and the fact that the diffusible component is in practice uniformly distributed throughout the aqueous phase; microemulsions therefore have the appearance of solutions but may exhibit the properties of emulsions as regards the partial pressure of the dispersed phase (paragraph 0047). One of ordinary skill would have had a reasonable expectation of success that the microemulsion would have a size less than 100 nm because Kunz teaches that microemulsions are further generally characterized by small average droplet sizes, from about 0.1 nm to about 200 nm, and in one embodiment have a diameter of less than about 100 nm. The Ostensen reference is included to show that microemulsion includes micelle. With regard to claims 28-30, the Office does not have the facilities for examining and comparing applicant's product with

the product of the prior art in order to establish that the product of the prior art does not possess the same functional characteristics of the claimed product. The claims are descriptive of the zeta potential of the assembly, and thus would be an inherent property of the claimed composition. In the absence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 U.S.P.Q.2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), *Ex parte Gray*, 10 USPQ2d 1922, 1923 (PTO Bd. Pat. App. & Int.) and *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). Since Eriksen teaches compositions meeting the structural requirements of the instant claims, it is interpreted absent evidence to the contrary that such formulations would be capable of achieving claimed functional property (zeta potential). Regarding claims 48 and 49, targeting ligand is recited as optional.

Conclusion

No claims are allowed at this time.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is (571)272-9928. The examiner can normally be reached on Monday-Wednesday 9 AM-5 PM and telework Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/LHS/

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618